

Cite this: *Chem. Sci.*, 2017, **8**, 2904

## Racemic hemiacetals as oxygen-centered pronucleophiles triggering cascade 1,4-addition/Michael reaction through dynamic kinetic resolution under iminium catalysis. Development and mechanistic insights†

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2-Hydroxydihydropyran-5-ones behave as excellent polyfunctional reagents able to react with enals through oxa-Michael/Michael process cascade under the combination of iminium and enamine catalysis. These racemic hemiacetalic compounds are used as unconventional O-pronucleophiles in the initial oxa-Michael reaction, also leading to the formation of a single stereoisomer under a dynamic kinetic resolution (DKR) process. Importantly, by using  $\beta$ -aryl or  $\beta$ -alkyl substituted  $\alpha,\beta$ -unsaturated substrates as initial Michael acceptors either kinetically or thermodynamically controlled diastereoisomers were formed with high stereoselection through the careful selection of the reaction conditions. Finally, a complete experimental and computational study confirmed the initially proposed DKR process during the catalytic oxa-Michael/Michael cascade reaction and also explained the kinetic/thermodynamic pathway operating in each case.

Received 2nd January 2017  
Accepted 28th January 2017

DOI: 10.1039/c7sc00009j  
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## Introduction

The asymmetric conjugate addition of heteroatom-centered nucleophiles to  $\alpha,\beta$ -unsaturated carbonyl compounds is one of the leading strategies for the enantio- and/or diastereoselective preparation of  $\beta$ -functionalized carbonyl compounds.<sup>1</sup> Moreover, the mechanistic profile associated to the conjugate addition reaction makes this transformation an excellent platform to develop cascade reactions.<sup>2</sup> This opens the possibility for the construction of complex molecular architectures from simple starting materials. With respect to stereocontrol, enantioselective catalysis, and more specifically, the proven ability of chiral secondary amines<sup>3</sup> to promote cascade reactions using enals as Michael acceptors, through the combination of the nowadays well established

iminium and enamine activation manifolds is a good example of the high level of sophistication achieved by this chemistry.<sup>4</sup>

In this sense, many examples of enantioselective cascade processes triggered by hetero-Michael reactions exist in the literature,<sup>5</sup> although reactions initiated by the conjugate addition of oxygen-centered nucleophiles remain scarce.<sup>6</sup> In fact, this type of reactions still represent one of the most challenging cases of conjugate addition of heteroatom-centered nucleophiles under organocatalytic activation because, in addition to reversibility issues, the typical oxygen-centered pronucleophiles, such as alcohols or carboxylic acids, typically show very poor reactivity towards Michael acceptors and normally undergo competitive 1,2-addition. Consequently, the reported examples of organocatalytic and enantioselective conjugate addition of oxygen pronucleophiles are limited to the use of oximes,<sup>7</sup> phenols,<sup>8</sup> enols,<sup>9</sup> alkoxyboronates,<sup>10</sup> hydroxylamines,<sup>11</sup> or peroxides<sup>12</sup> under iminium or H-bonding activation.<sup>13</sup> Organocatalytic cascade processes initiated by conjugate addition of O-nucleophiles have been mainly focused on the epoxidation of  $\alpha,\beta$ -unsaturated carbonyls with peroxides<sup>14</sup> and some limited examples of conjugate addition followed by aldol,<sup>15</sup> Mannich,<sup>16</sup> Henry,<sup>17</sup>  $\alpha$ -amination<sup>18</sup> and  $\alpha$ -fluorination<sup>19</sup> have also been published. However, with respect to 1,4-addition/Michael cascade processes, all cases reported are strictly limited to the use of aliphatic alcohols or phenols as oxygen-centered pronucleophiles (Scheme 1).<sup>20</sup>

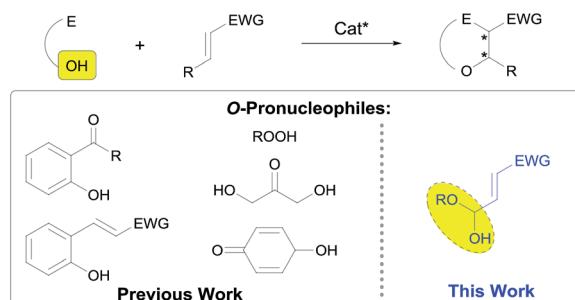
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† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization of all new compounds, including copies of NMR spectra and HPLC chromatograms traces, computational details and Cartesian coordinates of all stationary points. CCDC 1525188 (4i), 1525189 (6a) and 1525190 (9a). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7sc00009j





Scheme 1 Organocatalytic cascade processes initiated by conjugate addition of *O*-nucleophiles.

Consequently, we have focused our attention in the use of hemiacetals as potential pronucleophiles in cascade reactions initiated by 1,4-addition. Hemiacetals play a critical role in the chemistry of living cells and this type of compounds is also known to play the role of *O*-pronucleophiles in biochemical pathways of the secondary metabolism. In particular, the intramolecular conjugate addition of hemiacetals is typically associated with the stereodefined formation of acetal moieties in the total synthesis of complex natural products with relevant biological activities.<sup>21</sup> Remarkably, there is only one single example (a diastereoselective approach) that involves the use of a enantioenriched hemiacetal as Michael donor, performing with moderate stereocontrol.<sup>22</sup> On the other hand, the intramolecular conjugate addition of *in situ* generated hemiacetals using functionalized Michael acceptors that incorporate an internal alcohol moiety to assist the reaction has also been reported in both diastereo-<sup>23</sup> and enantioselective<sup>24</sup> fashion, although the latter relies on the stereocontrolled formation of the chiral hemiacetal moiety under catalyst control, that subsequently undergoes the intramolecular *O*-1,4-addition reaction. Finally, and quite recently, the catalytic and enantioselective intramolecular conjugate addition of peroxyhemiacetals to dienones has also been described.<sup>25</sup> Despite these advances, the conjugate addition of hemiacetal entities to electron-poor alkenes in an intermolecular fashion to initiate a cascade reaction is unprecedented in the chemical literature.

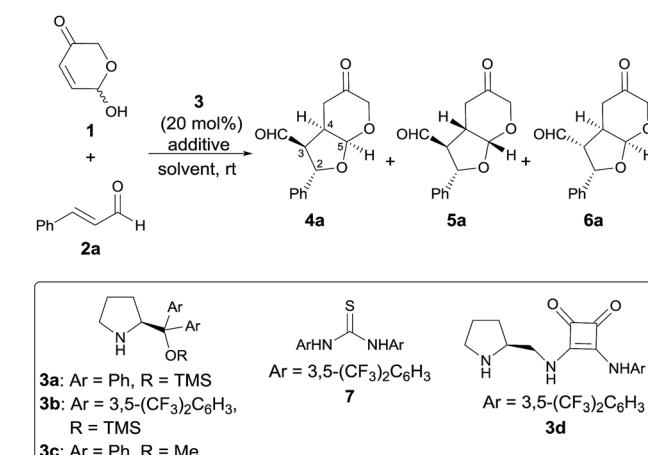
In particular, we wish to present herein a detailed study regarding the ability of hydroxypyranone **1** as an active chiral racemic *O*-pronucleophile that undergoes diastereo- and enantioselective cascade 1,4-addition/intramolecular Michael reaction with  $\alpha,\beta$ -unsaturated aldehydes in the presence of a chiral secondary amine catalyst, leading to the formation of bicyclic

furo[2,3-*b*]pyranes in a single step (Scheme 2). As far as we are aware of, this is the first example in which a hemiacetal shows its ability to participate as oxygen-based Michael donor in a stereoselective conjugate addition reaction under the combination of iminium and enamine activation manifolds. Moreover, this transformation occurs with the concomitant generation of up to four stereogenic centers in stereocontrolled way using a racemic starting material, in which a dynamic kinetic resolution (DKR) has also taken place to furnish the final adducts as highly enantio- and diastereoenriched compounds.

## Results and discussion

Our studies began by surveying reaction conditions for the projected transformation to proceed with the best yield and stereoselectivity employing (*E*)-cinnamaldehyde as model substrate (Table 1). We first tested the performance of the well-

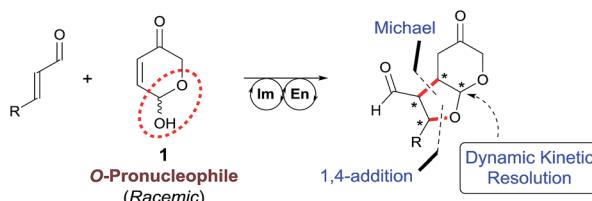
Table 1 Optimization of reaction conditions using hydroxypyranone **1** and aldehyde **2a** as model substrates<sup>a</sup>



Entry	3	Additive	Solvent	Yield <sup>b</sup> (%)	4a : 5a : 6a <sup>c</sup>	e.e. <sup>d</sup> (%)
1	<b>3a</b>	None	CHCl <sub>3</sub>	60	1 : 1 : 3	91/70/91
2	<b>3b</b>	None	CHCl <sub>3</sub>	<5	—	—
3	<b>3c</b>	None	CHCl <sub>3</sub>	43	1 : 2 : 3	n.d. <sup>e</sup> /38/50
4	<b>3a</b>	PhCO <sub>2</sub> H	CHCl <sub>3</sub>	46	1 : 1 : 3	90/60/95
5	<b>3a</b>	DABCO	CHCl <sub>3</sub>	67	1 : 1 : 1	90/78/90
6	<b>3a</b>	7	CHCl <sub>3</sub>	80	2 : 1 : 2	67/67/95
7 <sup>f</sup>	<b>3a</b>	7	CHCl <sub>3</sub>	74	<0.2 : 1 : 4	n.d. <sup>e</sup> /60/92
8	<b>3d</b>	None	CHCl <sub>3</sub>	<5	—	—
9 <sup>f</sup>	<b>3a</b>	7	Toluene	62	<0.2 : 1 : 5	n.d. <sup>e</sup> /20/94
10 <sup>f</sup>	<b>3a</b>	7	CH <sub>2</sub> Cl <sub>2</sub>	43	<0.2 : 1 : 3	n.d. <sup>e</sup> /38/90
11 <sup>f,g</sup>	<b>3a</b>	7	CHCl <sub>3</sub>	45	<0.2 : 1 : 2	n.d. <sup>e</sup> /60/95
12 <sup>f,h</sup>	<b>3a</b>	7	CHCl <sub>3</sub>	75	<0.2 : 1 : 4	n.d. <sup>e</sup> /64/93

<sup>a</sup> Reactions were carried out using 0.4 mmol of **1** and 0.2 mmol of **2a**, 20 mol% of catalyst **3** and 10 mol% of additive in 0.8 mL of CHCl<sub>3</sub> at rt for 18 h, followed by direct purification by flash chromatography.

<sup>b</sup> Combined yield for the mixture of diastereoisomers. <sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopy of crude reaction mixture. <sup>d</sup> Determined by HPLC after derivatization (see ESI). <sup>e</sup> n.d.: not determined. <sup>f</sup> Once the reaction was finished a 4 M HCl solution (2.0 mL) was added to the crude reaction mixture and this was stirred for further 4 h before standard work-up and purification. <sup>g</sup> Reaction carried out at 4 °C. <sup>h</sup> Reaction carried out at 45 °C.



Scheme 2 Enantioselective oxa-Michael/Michael cascade reaction between enals and hydroxypyranone **1**.



known O-TMS diphenylprolinol catalyst **3a**,<sup>26</sup> observing the formation of the expected bicyclic furo[2,3-*b*]pyranes as a mixture of three diastereoisomers out of the eight possible ones (Table 1, entry 1). An analysis of their stereostructure<sup>27</sup> showed that the reaction had proceeded with complete control at the C2 stereocenter, which indicated that the catalyst was able to perfectly control the facial selectivity in the initial 1,4-addition reaction. Compounds **4a** and **6a** differ on the absolute configuration of the stereochemically labile C3 stereocenter, assuming that the latter was formed after thermodynamic epimerization of the former (a detailed discussion will be provided in the following sections). Finally, the presence of diastereoisomer **5a** should be attributed to the participation of the other enantiomer of the racemic starting material **1**. It should be noted that an excess of hemiacetal **1** was used in order to achieve full conversion after 18 h but when the reaction was carried out using equimolar amounts of **1** and **2**, it proceeded with exactly the same diastereo- and enantiocontrol.<sup>28</sup> Moreover, in all cases, the recovered starting material **1** was found to be racemic. Consequently, the observed yield, the high (**6a** + **4a**)/**5a** ratio and the excellent e.e. obtained for **6a** is indicating that a kinetic resolution is operating throughout the overall reaction, which encouraged us to search for improved conditions that could favour the selective formation of major diastereoisomer **6a**. Consequently, we next tested the performance of modified catalyst **3b** (entry 2), but it was found to be inactive in this transformation, while the use of less bulky *O*-Me derivative **3c** turned into poorer enantiocontrol for the major product **6a** (entry 3). The incorporation of Brønsted acids or bases as additives did not end up in any significant improvement (entries 4 and 5). Remarkably, using achiral thiourea **7** as co-catalyst, which had been previously used by us for the activation of Michael acceptors in reactions under dienamine activation,<sup>29</sup> led to an important improvement in the yield of the reaction (entry 6). In addition, the formation of **4a** could be minimized by stirring the crude reaction mixture with aqueous HCl for 4 h to favour the thermodynamic equilibration of the **4a**/**6a** mixture (entry 7). We also tested bifunctional catalyst **3d**, not observing better results (entry 8). Other solvents (entries 9 and 10) and temperatures (entries 11 and 12) were also surveyed, without observing any significant improvement and therefore, it was concluded that the conditions summarized in entry 7 of Table 1 were the most appropriate ones for this transformation.

With the optimal conditions in hands, the scope of the reaction was studied with respect to the use of other  $\alpha,\beta$ -unsaturated aldehydes **2a-i**. As summarized in Table 2, the reaction proceeded well in all cases in which cinnamaldehyde derivatives incorporating either electron-withdrawing or electron-donating groups at the  $\beta$ -aryl substituent were employed (entries 1–7). In all these cases, adducts **6a–g** were isolated with good yields, high diastereoselectivities and as highly enantioenriched materials.  $\beta$ -Heteroaryl substituents were also well tolerated, observing that the reaction performed equally well in terms of chemical yield and stereocontrol (entry 8). On the other hand, when we turned to the use of a  $\beta$ -alkyl substituted enal such as 2-hexenal, a 1 : 1 : 2 mixture of the three diastereoisomers was obtained with an overall yield of 87% (entry 9).

Table 2 Scope of the reaction between cinnamaldehyde derivatives and hydroxypyranone **1**

Entry	<i>R</i> (product)	Yield (%)	5 : 6 <sup>a</sup>	
			5	6 <sup>b</sup> (%)
1	Ph ( <b>6a</b> )	74	1 : 4	95
2	4-(OMe)C <sub>6</sub> H <sub>4</sub> ( <b>6b</b> )	63	1 : 4	86
3	4-FC <sub>6</sub> H <sub>4</sub> ( <b>6c</b> )	73	1 : 2	92
4	4-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> ( <b>6d</b> )	78	1 : 2	92
5	4-BrC <sub>6</sub> H <sub>4</sub> ( <b>6e</b> )	87	1 : 1.5	88
6	2-(OMe)C <sub>6</sub> H <sub>4</sub> ( <b>6f</b> )	61	1 : 3	94
7	2-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> ( <b>6g</b> )	71	1 : 3	92
8	2-(Furyl) ( <b>6h</b> )	64	1 : 10	97
9	<i>n</i> -Pr ( <b>6i</b> )	87	1 : 2 <sup>c</sup>	84
10 <sup>d</sup>	<i>n</i> -Pr ( <b>4i</b> )	76	8 : 1 <sup>e</sup>	93 <sup>f</sup>

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy of crude reaction mixture.

<sup>b</sup> Determined by HPLC (see ESI). <sup>c</sup> Reaction also furnished diastereoisomer **4i** (**4i**/**5i**/**6i** ratio = 1 : 1 : 2). <sup>d</sup> Reaction conditions: catalyst **3c** (20 mol%), Cl<sub>3</sub>CCO<sub>2</sub>H (40 mol%) in CHCl<sub>3</sub> at rt. <sup>e</sup> **4i**/**5i** ratio is indicated. <sup>f</sup> e.e. of **4i** is given.

Unfortunately, in this case the acidic workup was ineffective for converting diastereoisomer **4i** into **6i**,<sup>30</sup> which also indicated that  $\beta$ -alkyl substituted enals behave differently from cinnamaldehyde derivatives with respect to diastereoselection. Remarkably, the formation of diastereoisomer **5** was negligible in all cases, which indicated that the DKR process was operating with high efficiency. We tried to improve the diastereoselectivity of the reaction between **2i** and **1**, by surveying other conditions but without any success (see ESI† for details). Remarkably, when catalyst **3c** was employed together with trichloroacetic acid as additive, the reaction again turned to be highly diastereo- and enantioselective, in this case favouring the formation of the kinetic product **4i** (entry 10). This product showed to be less prone to C3-epimerization compared with the cases in which  $\beta$ -aryl substituted enals were used and all attempts to induce the **4i** to **6i** isomerization under acidic or basic conditions led to decomposition.

Once we had realized that  $\beta$ -alkyl substituted enals required the use of catalyst **3c**, we proceeded to extend those conditions to a variety of substrates (Table 3). As it can be seen in this table, the reaction tolerates well the use of enals containing alkyl chains of different length and size, also observing that the yield of the process became only moderately affected when the length of the chain was considerably increased (entries 1–5). Aldehyde **2n** containing a bulkier non-linear alkyl chain also performed well, although enantioselectivity was slightly affected (compound **4n**) and a functionalized  $\alpha,\beta$ -unsaturated aldehyde such as **2o** also performed well, furnishing **4o** in good yield and stereocontrol (entry 7). Furthermore,  $\beta,\beta$ -disubstituted aldehyde **2p** was also reactive under these conditions, forming adduct **4p** in good yield, although with moderate



**Table 3** Scope of the reaction between  $\beta$ -alkyl substituted enals and hydroxypyranone **1**<sup>a</sup>

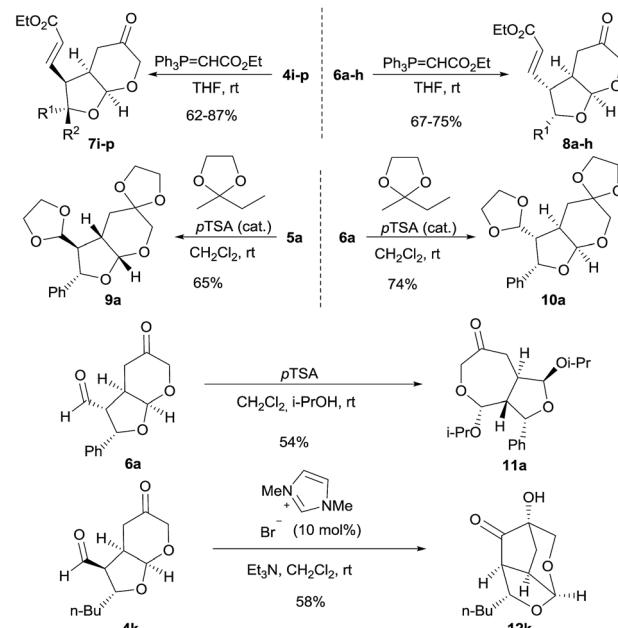
Entry	$R^1, R^2$ (product)	Yield (%)	4 : 5 <sup>a</sup>	
			e.e. 4 <sup>b</sup> (%)	e.e. 5 <sup>b</sup> (%)
1	<i>n</i> -Pr, H ( <b>4i</b> )	76	8 : 1	93
2	Et, H ( <b>4j</b> )	72	9 : 1	92
3	<i>n</i> -Bu, H ( <b>4k</b> )	69	11 : 1	94
4	<i>n</i> -C <sub>5</sub> H <sub>11</sub> , H ( <b>4l</b> )	73	5 : 1	95
5	<i>n</i> -C <sub>6</sub> H <sub>13</sub> , H ( <b>4m</b> )	61	7 : 1	96
6	<i>i</i> -Pr, H ( <b>4n</b> )	59	4 : 1	84
7	(Z)-EtCH=CH(CH <sub>2</sub> ) <sub>2</sub> , H ( <b>4o</b> )	60	5 : 1	96
8	Me, Me ( <b>4p</b> )	73	2 : 1	77

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy of crude reaction mixture.

<sup>b</sup> Determined by HPLC (see ESI).

diastereo- and enantioselectivity (entry 8). Contrary to the reaction with cinnamaldehyde derivatives shown before, the formation of diastereoisomer **6** was not observed in any of the cases. The absolute configuration of compounds **4l** and **6a** was unambiguously assigned by X-ray analysis and it was extended to all obtained products **4** and **6** based on mechanistic analogy.

Bicyclic furo[2,3-*b*]pyranes **4** and **6** showed to be somewhat unstable compounds because of their densely functionalized nature, and therefore, and for better characterization purposes, we accomplished their conversion into a more stable and easy-to-handle derivative after isolation. Attempts to carry out the selective reduction of the formyl group led to extensive decomposition but Wittig olefination took place smoothly leading to the formation of adducts **7i-p** and **8a-h** which were stable compounds that could be stored for several weeks without decomposition (Scheme 3). In addition, we also decided to explore some possible transformations to be carried out on the obtained bicyclic adducts, in order to illustrate their potential applications as chiral building blocks in organic synthesis. For example, the full protection of the formyl and the ketone moieties in adduct **6a** could be carried out by reaction with 2-ethyl-2-methyl-1,3-dioxolane under Brønsted acid catalysis yielding cleanly compound **10a**. This transformation was also carried out on the minor diastereoisomeric byproduct **5a**, isolating compound **9a** in good yield and for which crystals could be grown that also allowed the unequivocal assignment of its absolute configuration. Alternatively, the reaction of **6a** with *p*-TSA in propan-2-ol led to the formation of compound **11a** after an acid-catalyzed transketolization process, which took place with full chemoselectivity considering the presence of two chemically differentiated formyl units in the starting material. On the other hand, intramolecular benzoin condensation under NHC catalysis was also carried out on adduct **4k**, leading to compound **12k** which was isolated in good yield as a single diastereoisomer. This reaction involved the activation of the



**Scheme 3** Survey of transformations carried out on adducts **4**, **5** and **6**.

formyl moiety by condensation with the carbene catalysts followed by addition of the nucleophilic Breslow intermediate to the ketone moiety, generating a quaternary carbinol with complete diastereocontrol.

## Mechanistic considerations

In order to get a good mechanistic understanding on the behavior of the reaction, we decided to carry out a detailed experimental and computational study, mainly directed to understand the origin of the difference in the diastereoselectivity of this cascade process when  $\beta$ -aryl or  $\beta$ -alkyl-substituted Michael acceptors were employed as substrates, and also trying to understand the pathway operating in the resolution process, which is key for the very high stereocontrol. In this sense, and considering the presence of multiple reactive positions in the starting materials in which the amine catalyst can incorporate through either covalent bonding or *via* H-bonding interactions, we firstly carried out some experiments directed to discard the possible participation of complex reaction intermediates in which two or more molecules of the catalyst could be incorporated. In this sense, the process did not show any significant non-linear behavior when the reaction between **1** and **2a** using catalyst **3a** with a variable enantiopurity (Fig. 1). This is a clear indication that only one molecule of catalyst is involved in the rate determining step of the overall catalytic cycle.

We next moved to study the different mechanistic possibilities with the help of computational methods (for details see ESI†). Firstly, we set a preliminary computational study with an achiral system in order to establish the overall mechanistic picture and the preferred relative configuration of the products.



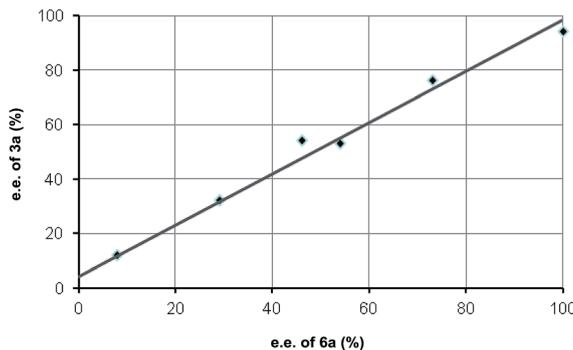


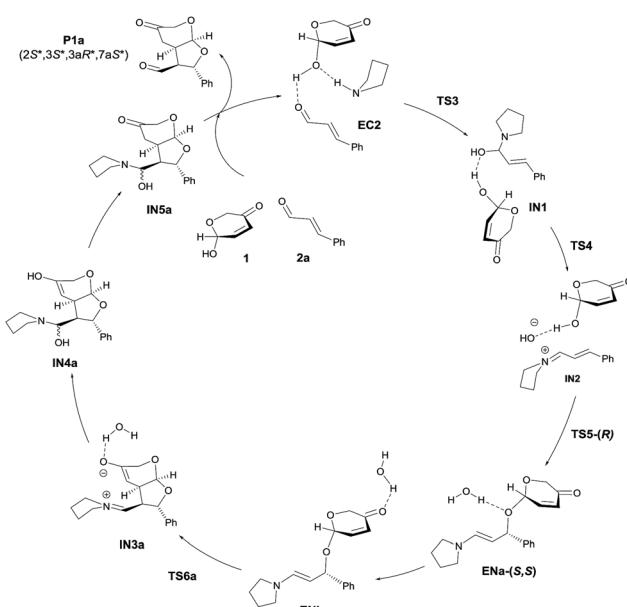
Fig. 1 Linear correlation between %ee of catalyst 3a and product 6a.

Considering that the reaction consists on a cascade 1,4-addition/Michael process we initially worked under the hypothesis that the first step should be considered as the stereodefining step of the overall process. We started by calculating the uncatalyzed background reaction between **1** and **2a**. But the energy barrier of the process was found to be  $20.0\text{ kcal mol}^{-1}$ . We also considered the participation of the catalyst by forming an encounter complex **EC1** with both aldehyde and alcohol without formation of the iminium salt as suggested by Lattanzi, and co-workers for the epoxidation of enones catalyzed by diarylprolinols.<sup>12c</sup> After formation of the encounter complex at  $-25.9\text{ kcal mol}^{-1}$ , the corresponding transition structure was located  $3.0\text{ kcal mol}^{-1}$  below the ground state (for details on these approaches see ESI†).

We next moved to study the reaction between **1** and **2a** under covalent activation by pyrrolidine following the well-known combination of iminium and enamine activation manifolds (Scheme 4). We arbitrarily chose the addition of hemiacetal (**R**-**1**) to the Si face of the iminium ion intermediate.<sup>31</sup> We also

considered the exclusive participation of the (*E,E*)-*s-trans* iminium species in agreement with previous reports.<sup>32</sup> Isomeric (*Z,E*)-iminium salts were also considered but they turned out to be more energetic, as expected (see ESI†). The study was initiated with the formation of encounter complex **EC2** (located at  $-22.3\text{ kcal mol}^{-1}$  with respect to the reactants) that can be considered as the initial point of a catalytic cycle in which both reactants are activated before the formation of the iminium ion. Evolution of **EC2** through **TS3** afforded hemiaminal **IN1** from which **IN2** is formed through **TS4** (energy barrier of **TS4**  $2.0\text{ kcal mol}^{-1}$ ) assisted by the hemiacetal reagent **1**. **IN2** should actually be regarded as a reactive complex formed by the iminium salt, the alcohol and the hydroxyl anion eliminated from the hemiaminal leading to the formation of the C–O bond through the initial conjugate addition. The corresponding transition structure **TS5**, leading to intermediate enamine **ENa**, was located at  $13.8\text{ kcal mol}^{-1}$  with respect to **EC2** ( $-8.5\text{ kcal mol}^{-1}$  with respect to the reagents). Such energy barrier is lower than alternative uncatalyzed **TS1** ( $20\text{ kcal mol}^{-1}$ ) and non-covalent activated **TS2** ( $-3.0\text{ kcal mol}^{-1}$ ), confirming that formation of **EC2** is the preferred starting point for the catalytic cycle. It should be taken into consideration that even in achiral series, the addition of two enantiomeric alcohols (**R**-**1** and **S**-**1**) by one face of the iminium ion renders two diastereomers. Consequently, this step is determinant for the diastereoselectivity of the reaction involving a kinetic resolution of the two alcohols. We determined during this preliminary analysis that **TS5-(R)**, consisting of the attack of **(R)-1** by the Si face of the iminium ion, was the preferred one leading to enamine **ENa-(S,S)** predicting a relative dr of *ca.* 4 : 1 with respect to the addition of **(S)-1** leading to **ENb-(S,R)** (for details see ESI†). Further discussion will be based on this preferred route. Once the initial 1,4-addition reaction has taken place, the second step of the cascade consists in an intramolecular Michael reaction between the enamine and the  $\alpha,\beta$ -unsaturated ketone moiety occurring after migration of the coordinated water (**ENa** to **ENb**). The intramolecular Michael reaction on enamine intermediate **ENb** can take place through the two diastereotopic faces of the pyranone scaffold<sup>33</sup> and consequently two transition structures can be found, from which **TS6a** (located at  $-15.3\text{ kcal mol}^{-1}$ ) was calculated to be the most stable one. Remarkably, these calculations also indicated that the initial 1,4-addition step (associated to **TS5**) resulted to be the rate-determining step of the overall reaction ( $\Delta G_{TS5} > \Delta G_{TS6a}$ ). Finally, regeneration of activated reactants in **EC2** from **IN3a** should take place through intermediates **IN4a** and **IN5**. The energy diagram for the catalytic cycle illustrated in Scheme 4 is given in Fig. 2. From this initial study carried out on this achiral model system it can be concluded that the preferred diastereoselectivity for the reaction will lead to the formation of the final product **P1a** with a relative  $2S^*, 3S^*, 3aR^*, 7aS^*$  configuration. The minor diastereomer ( $2S^*, 3S^*, 3aS^*, 7aR^*$ ) should be formed from the opposite enantiomer of the pronucleophile.

For the analysis of the selectivity of the reaction and prediction of the absolute configuration of the different products formed, the whole real system was considered, involving the participation of chiral catalyst **3a**. The study was restricted



Scheme 4 Calculated catalytic cycle for the model reaction between **1** and **2a** catalyzed by pyrrolidine (achiral model).



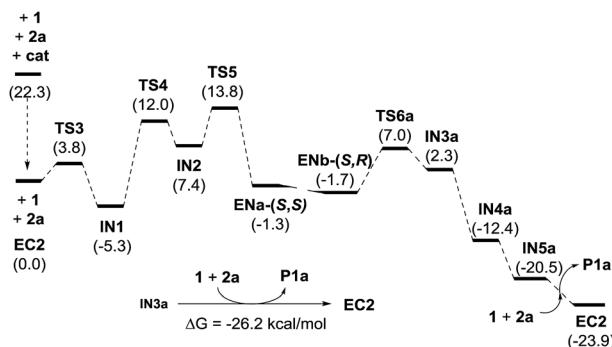
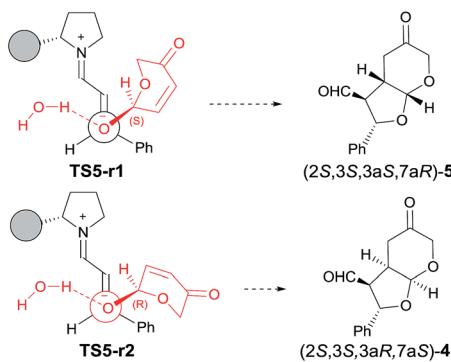


Fig. 2 Energy diagram of the catalytic cycle illustrated in Scheme 4.

to the key rate-limiting step found for the achiral model system, *i.e.* the 1,4-addition of hemiacetal **1** to the iminium ion derived from **2a**, since the size of the model is in the limit of computational resources.<sup>34</sup> Catalyst **3a** is known to operate according to a steric model<sup>26,35</sup> in reactions proceeding through both enamine and iminium intermediates, and particularly when these intermediates are involved in Michael-type reactions.<sup>36</sup> As a consequence, only the attack through the less hindered faces of these intermediates (iminium ion or enamine) have been considered in agreement with previous calculations for other reactions.<sup>26</sup> We also considered the (*E*)-iminium ion (with respect to C=N bond) as the most reactive isomer according to previous reports by Seebach and co-workers.<sup>35</sup> Therefore and for the complete study, we considered as possible variable structural parameters, the participation of the catalyst through north and south conformations at the pyrrolidine ring, two different diastereoisomers (*Z* and *E*) of the C=C bond of the iminium ion intermediate (resulting into the reaction with the Michael donor **1** through a different facial selectivity) and the participation of the two enantiomeric hemiacetal reagents **1** (in order to evaluate kinetic resolution). Thus, a total of 8 TS were located and characterized (see ESI† for details). Boltzmann analysis for these transition structures predicted a 91 : 9 ratio of products **4** : **5**, in good agreement with experimental observations (considering that product **4** subsequently epimerizes onto **6**, see below). The two preferred transition structures **TS5-r1** and

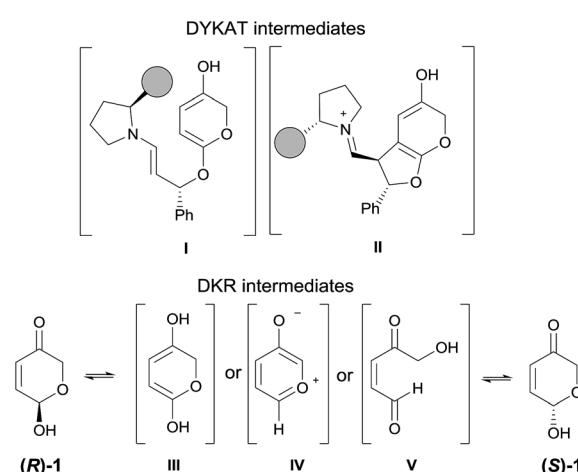
Fig. 3 TS structures leading to compounds **4** and **5**.

**TS5-r2** leading to **5** and **4**, respectively, are shown in Fig. 3 (for geometries see ESI†).

The difference in energy of 1.6 kcal mol<sup>-1</sup> observed between **TS5-r1** and **TS5-r2** can be explained on the basis of a combination of electronic effects and steric interactions. In fact, 1,4-addition is facilitated by the loss of the proton of the OH group of the hemiacetal to form a water molecule upon combination with the hydroxyl anion. NCI analysis (see ESI†) shows that, in the transition state, the negative charge is located between the water oxygen atom and the attacking oxygen of **1** (actually, most of the negative charge is located at the oxygen atom of **1**; which should be interpreted as the driving force for the nucleophilic attack). The partial negative charge located at the incipient water molecule should be close to the iminium nitrogen atom which has a partial positive charge. This electrostatic interaction forces the orientation of the attack of the hydroxyl group, which should release the proton to form water. According to this model calculations predict a kinetic resolution in favour of the attack of (*R*)-**1** to give compound **4** (which might epimerize, see below) as the major isomer.

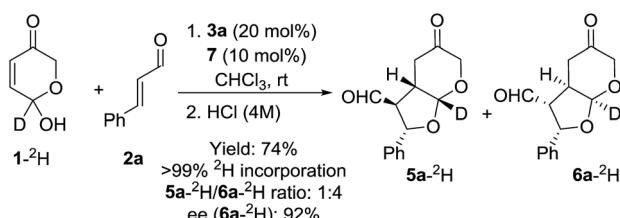
The mechanistic picture presented up to this moment involves the occurrence of a DKR process through the fast racemization of the starting hemiacetal reagent **1** before it gets involved in the cascade 1,4-addition/Michael reaction.<sup>37</sup> However, a potential DYKAT cannot be discarded as the epimerization of the 7a position could also take place after the 1,4-addition process (through the potential formation of a dienol intermediate under the intermediacy of the Brønsted acid co-catalyst **7**, see DYKAT intermediates **I** and **II** in Scheme 5). In order to rule out this possibility, the resolution process of the starting hydroxypyranone **1** was studied experimentally. For this purpose, we carried out the reaction between cinnamaldehyde (**2a**) and deuterated hydroxypyranone **1** under optimized conditions, observing the formation of products **5a**-<sup>2</sup>H and **6a**-<sup>2</sup>H in good yield and with an excellent enantiocontrol (Scheme 6).

The fact that the deuterium atom present at the starting material had been preserved in the same position across the



Scheme 5 Possible intermediates involved in the kinetic resolution process.





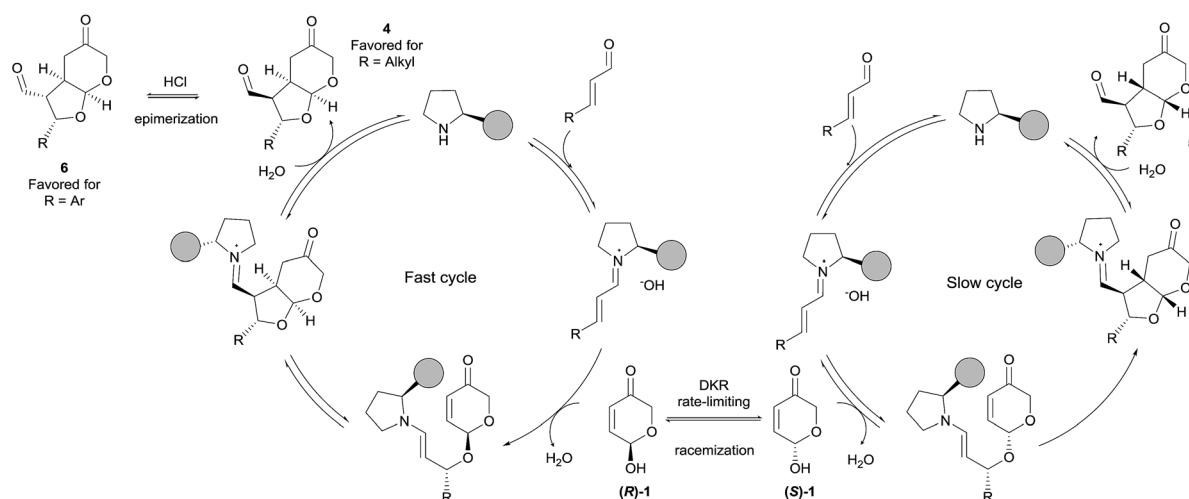
Scheme 6 Study of the resolution process.

overall cascade reaction confirmed our initial hypothesis that a DKR process was operating and that the possible intermediates that could operate through a hypothetical DYKAT process (DYKAT intermediates **I** and **II**) were not formed in the reaction. The racemization of the starting material could eventually occur through the participation of dienol intermediate **III**, through oxidopyrylium ylide **IV** or, alternatively, *via* ring-opening of the hemiacetal moiety through intermediate **V**. The experiment using deuterated substrate **1** shown in Scheme 6 directly rules out the possible participation of intermediate **III**, but it does not provide any evidence to support the participation of either **IV** or **V**. In order to discern between **IV** and **V** as the intermediates involved in the racemization process we carried out another computational study through the several channels involving those intermediates and under the intermediacy of the Brønsted acid. For that purpose, this process was initially modelled by using formic acid as promoter of the reaction.

From the several paths studied (see ESI† for details) there is a clear preference for the open-chain intermediate **V** which is located at 3.5 kcal mol<sup>-1</sup> with respect to compound **1**. Intermediate **IV** is located at 20 kcal mol<sup>-1</sup>. The corresponding barriers leading to **V** and **IV** were found to be 11.9 and 21.3 kcal mol<sup>-1</sup>, respectively. We also calculated a more realistic transition structure leading to intermediate **V** promoted by either water or thiourea **7** for which energy barriers of 21.1 and

28.8 kcal mol<sup>-1</sup> were found (see ESI†). Consequently, this computational study shows that the calculated barrier for the racemization of **1** is 11.9 kcal mol<sup>-1</sup>, which is lower than the following rate-determining step (13.8 kcal mol<sup>-1</sup>) associated to the oxa-Michael/Michael cascade sequence, thus being consistent with a DKR process. The proposed racemization of **1** through an open-chain intermediate is in good agreement with highly accurate recent studies on mutarotation of D-glucose in water as a solvent.<sup>38</sup>

Taking into account all experimental and computational investigations, we propose a catalytic cycle (Scheme 7) based on the known iminium/enamine activation manifold starting with the conjugate addition of the hemiacetal moiety of pyranone **1** with the intermediate iminium ion that installs the first stereocenter and in which one of the enantiomers of **1** is reacting faster than the other. This type of 1,4-additions of O-nucleophiles with enals under iminium activation has been proposed to be reversible processes,<sup>39</sup> which means that in our case it must be followed by a fast intramolecular Michael reaction that generates the other two stereocenters. Once the product has been released and catalyst regenerated, preferential formation of diastereoisomer **4** (2S, 3S, 3aR, 7aS) as the major one, and compound **5** (2S, 3S, 3aS, 7aR) as the minor one. However, when  $\beta$ -aryl substituted enals were employed as substrates mixtures of **5** and **6** were experimentally obtained, the latter having a (2S, 3R, 3aS, 7aR) configuration, and being this isomer obtained almost exclusively after *in situ* acidic treatment (see Table 2). This behaviour, together with the data obtained by calculations suggests that, once isomer **4** is formed, it undergoes fast epimerization at the  $\alpha$ -position to the formyl substituent. Experimentally, epimerization of **4** into **6** has been observed under acidic conditions for those substrates containing aryl substituents ( $R = \text{Ph}$ ). On the other hand, for adducts incorporating alkyl substituents at that position ( $R = \text{Et}$ ), epimerization was observed in rather less extent after treatment with hydrochloric acid, and no epimerization at all was detected



Scheme 7 Proposed catalytic cycles for DKR.



when the reaction was carried out in the presence of trichloroacetic acid.<sup>40</sup>

In order to understand this atypical behaviour, an exhaustive conformational analysis showed that epimerization of **4** into **6** is thermodynamically favoured independently of the nature (aromatic *vs.* aliphatic) of the substituent. This **4** to **6** epimerization process was subsequently studied in detail using DFT calculations in order to determine the energy barrier and to analyze the kinetics of the process (see ESI†). The preferred pathway corresponds to the formation of (*E*)-enols and energy barriers showed that epimerization of adducts containing an aryl substituent (*R* = Ph) is favoured by 1.5 kcal mol<sup>-1</sup> with respect to those containing an alkyl group at the same position (*R* = Et). Accordingly, epimerization of **4a** is kinetically favoured and it should be expected that epimerization of **4a** to **6a** takes place faster than that of **4j** to **6j**.

A complete epimerization could not be achieved in the reaction of aliphatic enals because they tend to decompose under treatment with aqueous HCl. Indeed, by using 1 M HCl ( $pK_a < 1$ ) a slower epimerization was observed for **4j** (see Table 2, entry 9) with respect to **4a**, which epimerized completely. Other acids like benzoic acid ( $pK_a = 4.19$ ) and trichloroacetic acid ( $pK_a = 0.77$ ) were not acidic enough to promote epimerization at an appreciable rate. In fact, modelization using formic acid ( $pK_a = 3.75$ ) provided energy barriers of *ca.* 22 kcal mol<sup>-1</sup> which are in the limit for a spontaneous process at room temperature (see ESI†).<sup>41</sup>

## Conclusions

The enantio- and diastereoselective synthesis of furopyranes has been developed through a transformation that operates under a dynamic kinetic resolution process of involving a hemiacetal reagent as unconventional oxygen-centered Michael donor that undergoes oxa-Michael/Michael cascade reaction with enals in the presence of a chiral secondary amine catalyst. This transformation constitutes a rare example of cascade iminium/enamine reaction with an unconventional oxygen pronucleophile that involves the stereocontrolled formation of one single enantiomer over 16 possible stereoisomers. Experimental studies together with computational methods demonstrate that the initial racemization of the hemiacetal occurs through an open-chain pathway before the catalytic cycle takes place. A final epimerization in the stereocenter incorporating the formyl group also takes place when the thermodynamically more stable compound can be isolated without decomposition.

## Acknowledgements

This research was supported by the Spanish MINECO (FEDER-CTQ2014-52107-P, FEDER-CTQ2013-44367-C2-1-P and FEDER-CTQ2016-76155-R), the Basque Government (Grupos IT908-16), UPV/EHU (UFI QOSYC 11/22) and Government of Aragón (Grupos Consolidados, E.10). D. R.-L. thanks MEC for a pre-doctoral FPU fellowship. The authors thankfully acknowledge the resources from the supercomputers "Memento" and

"Cierzo", technical expertise and assistance provided by BIFI-ZCAM (Universidad de Zaragoza, Spain).

## Notes and references

- (a) E. Reyes, U. Uria, J. L. Vicario and L. Carrillo, *Org. React.*, 2016, **90**, 1; (b) *Catalytic Asymmetric Conjugate Reactions*, ed. A. Cordova, Wiley-VCH, Weinheim, 2010; (c) *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and Y. Yamamoto, Springer-Verlag, Berlin, vol. 3, 1999.
- For some selected reviews, see: (a) Y. Hayashi, *Chem. Sci.*, 2016, **7**, 866; (b) J. Muzart, *Tetrahedron*, 2013, **69**, 6735; (c) H. Pellissier, *Chem. Rev.*, 2013, **113**, 442; (d) C. J. Ball and M. C. Willis, *Eur. J. Org. Chem.*, 2013, 425; (e) E. Ricca, B. Brucher and J. H. Schrittwieser, *Adv. Synth. Catal.*, 2011, **353**, 2239; (f) E. A. Anderson, *Org. Biomol. Chem.*, 2011, **9**, 3997; (g) T. Vlaar, E. Ruijter and R. V. A. Orru, *Adv. Synth. Catal.*, 2011, **353**, 809; (h) K. C. Nicolaou and J. S. Chen, *Chem. Soc. Rev.*, 2009, **38**, 2993.
- For some selected reviews specifically focused on aminocatalysis, see: (a) B. M. Paz, H. Jiang and K. A. Jørgensen, *Chem.-Eur. J.*, 2015, **21**, 1846; (b) M. C. Holland and R. Gilmour, *Angew. Chem., Int. Ed.*, 2015, **54**, 3862; (c) P. Melchiorre, *Angew. Chem., Int. Ed.*, 2012, **51**, 9748; (d) P. Melchiorre, M. Marigo, A. Carloni and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138; (e) B. List, *Chem. Commun.*, 2006, 819.
- For some reviews, see: (a) C. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390; (b) Y.-C. Chen and H.-L. Cui, *Organocatalytic Cascade Reactions in Science of Synthesis, Asymmetric Organocatalysis*, ed. B. List and K. Maruoka, Thieme: Stuttgart, 2012, vol. 2, p. 787; (c) D. Bonne, T. Constantieux, Y. Coquerel and J. Rodriguez, *Org. Biomol. Chem.*, 2012, **10**, 3969; (d) H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 237; (e) A. Grossmann and D. Enders, *Angew. Chem., Int. Ed.*, 2012, **51**, 314; (f) B. Westermann, M. Ayaz and S. S. van Berkel, *Angew. Chem., Int. Ed.*, 2010, **49**, 846; (g) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167.
- For reviews, see: (a) Z. Galestokova and R. Sebesta, *Eur. J. Org. Chem.*, 2012, 6688; (b) M. Ruiz, P. Lopez-Alvarado, G. Giorgi and J. C. Menendez, *Chem. Soc. Rev.*, 2011, **40**, 3445; (c) D. Bonne, Y. Coquerel, T. Constantieux and J. Rodriguez, *Tetrahedron: Asymmetry*, 2010, **21**, 1085; (d) H. Lebel, J. F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977; (e) D. Caine, *Tetrahedron*, 2001, **57**, 2643.
- (a) C. F. Nising and S. Bräse, *Chem. Soc. Rev.*, 2012, **41**, 988; (b) C. F. Nising and S. Bräse, *Chem. Soc. Rev.*, 2008, **37**, 1218.
- (a) S. Bertelsen, P. Diner, R. L. Johansen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2007, **129**, 1536; (b) A. Pohjakallio, P. M. Pihko and U. M. Laitinen, *Chem.-Eur. J.*, 2010, **16**, 11325; (c) F.-L. Liu, J.-R. Chen, B. Feng, X.-Q. Hu, L.-H. Ye, L.-Q. Lu and W.-J. Xiao, *Org. Biomol. Chem.*, 2014, **12**, 1057.
- (a) Y. Kobayashi, R. Kuramoto and Y. Takemoto, *Beilstein J. Org. Chem.*, 2015, **11**, 2654; (b) Y.-L. Zhang and Y.-Q. Wang, *Tetrahedron Lett.*, 2014, **55**, 3255; (c) P. H. Poulsen, K. S. Feu, B. M. Paz, F. Jensen and





K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2015, **54**, 8203; for the use of heteroaromatic alcohols see: (d) A. K. Ghosh, X. Cheng and B. Zhou, *Org. Lett.*, 2012, **14**, 5046; (e) D. Enders, A. Grossmann, B. Gieraths, M. Duezdemir and C. Merkens, *Org. Lett.*, 2012, **14**, 4254; (f) E. Sekino, T. Kumamoto, T. Tanaka, T. Ikeda and T. Ishikawa, *J. Org. Chem.*, 2004, **69**, 2760.

9 B. Parhi, J. Gurjar, S. Pramanik, A. Midya and P. Ghorai, *J. Org. Chem.*, 2016, **81**, 4654.

10 (a) B. Ravindra, S. Maity, B. G. Das and P. Ghorai, *J. Org. Chem.*, 2015, **80**, 7008; (b) T. Azuma, A. Murata, Y. Kobayashi, T. Inokuma and Y. Takemoto, *Org. Lett.*, 2014, **16**, 4256.

11 (a) Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2013, **52**, 11114; (b) R. Noël, V. Gembus, V. Levacher and J.-F. Briere, *Org. Biomol. Chem.*, 2014, **12**, 1245; (c) Q.-Y. Dou, Y.-Q. Tu, Y. Zhang, J.-M. Tian, F.-M. Zhang and S.-H. Wang, *Adv. Synth. Catal.*, 2016, **358**, 874.

12 (a) C. M. Reisinger, X. Wang and B. List, *Angew. Chem., Int. Ed.*, 2008, **47**, 8112; (b) X. Lu, Y. Liu, B. Sun, B. Cindric and L. Deng, *J. Am. Chem. Soc.*, 2008, **130**, 8134. See also: (c) A. Russo and A. Lattanzi, *Adv. Synth. Catal.*, 2008, **350**, 1991.

13 Some examples regarding the use of aliphatic alcohols as O-pronucleophiles in intramolecular versions: (a) Y. Fukata, R. Miyaji, T. Okamura, K. Asano and S. Matsubara, *Synthesis*, 2013, **45**, 1627; (b) Y. Lu, G. Zou and G. Zhao, *ACS Catal.*, 2013, **3**, 1356; (c) W. Wu, X. Li, H. Huang, X. Yuan, J. Lu, K. Zhu and J. Ye, *Angew. Chem., Int. Ed.*, 2013, **52**, 1743; (d) M. O. Ratnikov, L. E. Farkas and M. P. Doyle, *J. Org. Chem.*, 2012, **77**, 10294; for an earlier example of attempted amine-catalyzed conjugate addition of aliphatic alcohols to enals furnishing low levels of enantioselection, see: (e) D. Díez, M. G. Nuñez, A. Benéitez, R. F. Moro, I. S. Marcos, P. Basabe, H. Broughton and J. G. Urones, *Synlett*, 2009, 390; (f) T. Kano, Y. Tanaka and K. Maruoka, *Tetrahedron*, 2007, **63**, 8658.

14 (a) O. Lifchits, M. Mahlau, C. M. Reisinger, A. Lee, C. Fares, I. Polyak, G. Gopakumar, W. Thiel and B. List, *J. Am. Chem. Soc.*, 2013, **135**, 6677; (b) M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 6964; (c) S. Lee and D. W. C. MacMillan, *Tetrahedron*, 2006, **62**, 11413; (d) C. Sparr, W. B. Schweizer, H. M. Senn and R. Gilmour, *Angew. Chem., Int. Ed.*, 2009, **48**, 3065; (e) X. Lu, Y. Liu, B. Sun, B. Cindric and L. Deng, *J. Am. Chem. Soc.*, 2008, **130**, 8134; (f) X. Wang, C. M. Reisinger and B. List, *J. Am. Chem. Soc.*, 2008, **130**, 6070; (g) J. Vesely, I. Ibrahim, G.-L. Zhao, R. Rios and A. Cordova, *Angew. Chem., Int. Ed.*, 2007, **46**, 778; (h) F. Pesciaioli, F. De Vicentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2008, **47**, 8703; (i) A. Armstrong, C. A. Baxter, S. G. Lamont, A. R. Pape and R. Wincewicz, *Org. Lett.*, 2007, **9**, 351; (j) E. J. Corey and F.-Y. Zhang, *Org. Lett.*, 1999, **1**, 1287.

15 (a) J. Zhang, M. J. Ajitha, L. He, K. Liu, B. Dai and K.-W. Huang, *Adv. Synth. Catal.*, 2015, **357**, 967; (b) Y.-H. Feng, R.-S. Luo, L. Nie, J. Weng and G. Lu, *Tetrahedron: Asymmetry*, 2014, **25**, 523; (c) J. Aleman, C. Alvarado, V. Marcos, A. Nunez and J. L. Garcia-Ruano, *Synthesis*, 2011, 1840; (d) C.-L. Liu, X.-S. Zhang, R. Wang and W. Wang, *Org. Lett.*, 2010, **12**, 4948; (e) B. C. Das, S. Mohapatra, P. D. Campbell, S. Nayak, S. M. Mahalingam and T. Evans, *Tetrahedron Lett.*, 2010, **51**, 2567; (f) S.-P. Luo, Z.-B. Li, L.-P. Wang, Y. Guo, A.-B. Xia and D.-Q. Xu, *Org. Biomol. Chem.*, 2009, **7**, 4539; (g) E. Reyes, G. Talavera, J. L. Vicario, D. Badia and L. Carrillo, *Angew. Chem., Int. Ed.*, 2009, **48**, 5701; (h) T. Govender, L. Hojabri, F. M. Moghaddam and P. I. Arvidsson, *Tetrahedron: Asymmetry*, 2006, **17**, 1763; (i) S. Sunden, I. Ibrahim, G.-L. Zhao, A. Eriksson and A. Cordova, *Chem.-Eur. J.*, 2007, **13**, 574.

16 (a) J. Aleman, A. Nunez, L. Marzo, V. Marcos, C. Alvarado and J. L. Garcia Ruano, *Chem.-Eur. J.*, 2010, **16**, 9453; (b) A.-B. Xia, D.-Q. Xu, S.-P. Luo, J.-R. Jiang, J. Tang, Y.-F. Wang and Z.-Y. Xu, *Chem.-Eur. J.*, 2010, **16**, 801.

17 (a) B. Zheng, W. Hou and Y. Peng, *ChemCatChem*, 2014, **6**, 2527; (b) G. Yin, R. Zhang, L. Li, J. Tian and L. Chen, *Eur. J. Org. Chem.*, 2013, 5431; (c) Z. Zhang, G. Jakab and P. R. Schreiner, *Synlett*, 2011, 1262.

18 J. Weng, L.-J. Huang, L. Long, L.-Y. Xu and G. Lu, *Tetrahedron Lett.*, 2016, **57**, 2554.

19 H.-F. Wang, H.-F. Cui, Z. Chai, P. Li, C.-W. Zheng, Y.-Q. Yang and G. Zhao, *Chem.-Eur. J.*, 2009, **15**, 13299.

20 (a) P. Saha, A. Biswas, N. Molleti and V. K. Singh, *J. Org. Chem.*, 2015, **80**, 11115; (b) A.-B. Xia, C. Wu, T. Wang, Y.-P. Zhang, X.-H. Du, A.-G. Zhong, D.-Q. Xu and Z.-Y. Xu, *Adv. Synth. Catal.*, 2014, **356**, 1753; (c) Y. Huang, C. Zheng, Z. Chai and G. Zhao, *Adv. Synth. Catal.*, 2014, **356**, 579; (d) H. Mao, A. Lin, Y. Tang, Y. Shi, H. Hu, Y. Cheng and C. Zhu, *Org. Lett.*, 2013, **15**, 4062; (e) M. T. Corbett and J. S. Johnson, *Chem. Sci.*, 2013, **4**, 2828; (f) P. G. McGarraugh and S. E. Brenner-Moyer, *Org. Lett.*, 2011, **13**, 6460; (g) H. Wang, J. Luo, X. Han and Y. Lu, *Adv. Synth. Catal.*, 2011, **353**, 2971; (h) L. Zu, S. Zhang, H. Xie and W. Wang, *Org. Lett.*, 2009, **11**, 1627; (i) F.-L. Zhang, A.-W. Xu, Y.-F. Gong, M.-H. Wei and X.-L. Yang, *Chem.-Eur. J.*, 2009, **15**, 6815.

21 For some selected examples, see: (a) K. C. Nicolaou, E. A. Theodorakis, F. P. J. T. Rutjes, J. Tiebes, M. Sato, E. Untersteller and X.-Y. Xiao, *J. Am. Chem. Soc.*, 1995, **117**, 1171; (b) R. M. de Figueiredo, R. Fröhlich and M. Christmann, *Angew. Chem., Int. Ed.*, 2007, **46**, 2883; (c) L. K. Geisler, S. Nguyen and C. J. Forsyth, *Org. Lett.*, 2004, **6**, 4159; (d) S. Sommer and H. Waldmann, *Chem. Commun.*, 2005, 5684; (e) M. T. Crimmins and P. Siliphaiwanh, *Org. Lett.*, 2003, **5**, 4641; (f) C. F. Nising, U. K. Ohnemüller and S. Bräse, *Angew. Chem., Int. Ed.*, 2006, **45**, 307; (g) A. Matviitsuk, F. Berndt and R. Mahrwald, *Org. Lett.*, 2014, **16**, 5474; (h) D. A. Evans, P. Nagorny, D. J. Reynolds and K. J. McRae, *Angew. Chem., Int. Ed.*, 2007, **46**, 541; (i) T. A. Dineen and W. R. Roush, *Org. Lett.*, 2004, **6**, 2043; (j) D. T. Hung, J. B. Nerenberg and S. L. Schreiber, *J. Am. Chem. Soc.*, 1996, **118**, 11054.

22 C. Xong, A. Ovens, W. Pilling, J. W. Ward and D. J. Dixon, *Org. Lett.*, 2008, **10**, 565.

23 For some examples, see: (a) D. A. Evans and J. A. Gauchet-Prunet, *J. Org. Chem.*, 1993, **58**, 2446; (b) P. A. Evans, A. Grisin and M. J. Lawler, *J. Am. Chem. Soc.*, 2012, **134**, 2856; (c) A. Grisin, S. Oliver, M. D. Ganton, J. Bacsa and P. A. Evans, *Chem. Commun.*, 2015, **51**, 15681; (d) L. Becerra-Figueroa, E. Brun, M. Mathieson, L. J. Farrugia, C. Wilson, J. Prunet and D. Gamba-Sanchez, *Org. Biomol. Chem.*, 2017, **15**, 301.

24 (a) T. Okamura, K. Asano and S. Matsubara, *Chem. Commun.*, 2012, **48**, 5076; (b) A. Matsumoto, K. Asano and S. Matsubara, *Chem. Commun.*, 2015, **51**, 11693; (c) N. Yoneda, A. Hotta, K. Asano and S. Matsubara, *Org. Lett.*, 2014, **16**, 6264.

25 (a) D. M. Rubush, M. A. Morges, B. J. Rose, D. H. Thamm and T. Rovis, *J. Am. Chem. Soc.*, 2012, **134**, 13554; (b) S. Maity, B. Parhi and P. Ghorai, *Angew. Chem., Int. Ed.*, 2016, **55**, 7723.

26 First reports: (a) M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 794; (b) H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed.*, 2005, **44**, 4212. For some reviews: (c) B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2015, **54**, 13860; (d) S. Meninno and A. Lattanzi, *Chem. Commun.*, 2013, **49**, 3821; (e) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht and K. A. Jørgensen, *Acc. Chem. Res.*, 2012, **45**, 248; (f) A. Mielgo and C. Palomo, *Chem.-Asian J.*, 2008, **3**, 922.

27 Determined by X-ray analysis of several adducts prepared when extending the reaction to other enals see ESI.†

28 Yields were typically 10–15% lower when the reaction was quenched at the same time using **1** and **2** in a 1 : 1 ratio.

29 (a) E. Reyes, G. Talavera, J. L. Vicario, D. Badia and L. Carrillo, *Angew. Chem., Int. Ed.*, 2009, **48**, 5701; (b) N. Z. Burns, M. R. Witten and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2011, **133**, 14578; (c) M. R. Witten and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2014, **53**, 5912.

30 Stirring a purified sample of compound **4i** in different acidic media (aqueous or water-free) led to decomposition of the product, only detecting the presence of traces of the desired diastereoisomer **6i** after few minutes.

31 Water was selected as model structure of the Brønsted acid cocatalyst (either trichloroacetic acid or thiourea **7**) because it is a more computationally tractable surrogate that can be used in a neutral form conserving both donor and acceptor H-bond capabilities. Introduction of a carboxylate anion would cause unbalance of charges that would introduce significant errors in calculations. For the reactions using thiourea **7** as additive, this has no effect on the stereoselectivity.

32 (a) D. Seebach, U. Groselj, D. M. Badine, W. B. Schweizer and A. K. Beck, *Helv. Chim. Acta*, 2008, **91**, 1999; (b) U. Groselj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, I. Krossing, P. Klose, Y. Hayashi and T. Uchimaru, *Helv. Chim. Acta*, 2009, **92**, 1225.

33 Technically, the two faces of the enamine should also be considered but this is not possible due to steric hindrance.

34 The fully optimized structures for the real system using cc-pVTZ basis set resulted in 1808 basis functions. For a discussion on current advances and limits in computational methods, see: A. Armstrong, R. A. Boto, P. Dingwall, J. Contreras-Garcia, M. J. Harvey, N. J. Mason and H. S. Rzepa, *Chem. Sci.*, 2014, **5**, 2057.

35 Y. Hayashi, D. Okamura, T. Yamazaki, Y. Ameda, H. Gotoh, S. Tsuzuki, T. Uchimaru and D. Seebach, *Chem.-Eur. J.*, 2014, **20**, 17077.

36 (a) S. Bertelsen, M. Marigo, S. Brandes, P. Diner and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2006, **128**, 12973; (b) S. Reboreda, E. Reyes, J. L. Vicario, D. Badia, L. Carrillo, A. Cozar and F. Cossio, *Chem.-Eur. J.*, 2012, **18**, 7179. See also ref. 26.

37 For examples regarding the use of dihydropyranone acetals undergoing DKR processes, see: (a) A. Orue, E. Reyes, J. L. Vicario, L. Carrillo and U. Uria, *Org. Lett.*, 2012, **14**, 3740; (b) H.-Y. Wang, K. Yang, S. R. Bennett, S. Guo and W. Tang, *Angew. Chem., Int. Ed.*, 2015, **54**, 8756.

38 (a) A. M. Silva, E. C. da Silva and C. O. da Silva, *Carbohydr. Res.*, 2006, **341**, 1029, and references cited therein; (b) S. Morpugo, A. Grandi, C. Zazza and M. Bossa, *THEOCHEM*, 2005, **729**, 71; (c) X. Qian, *J. Phys. Chem. B*, 2013, **117**, 11460; for a definitive computational demonstration by using molecular simulations based on the combination of DFT methodology with the molecular dynamics formalism, see: (d) W. Plazinski, A. Plazinska and M. Drach, *Phys. Chem. Chem. Phys.*, 2015, **17**, 21622.

39 P. G. McGarraugh, R. C. Johnston, A. Martinez-Muñoz, P. H.-Y. Cheong and S. E. Brenner-Moyer, *Chem.-Eur. J.*, 2012, **18**, 10742, see also ref. 20f.

40 Adducts with bulkier alkyl substituents at this position decomposed upon treatment with aqueous HCl.

41 A process with an energy barrier of 20 kcal mol<sup>-1</sup> has an interconversion rate (*k*) of  $1.3 \times 10^{-2}$  s<sup>-1</sup> at 25 °C, *i.e.* a half-life  $\tau_{1/2}$  of 53 seconds. (half-life  $\tau_{1/2}$  is the time it takes 50% of the molecules to cross the barrier).

